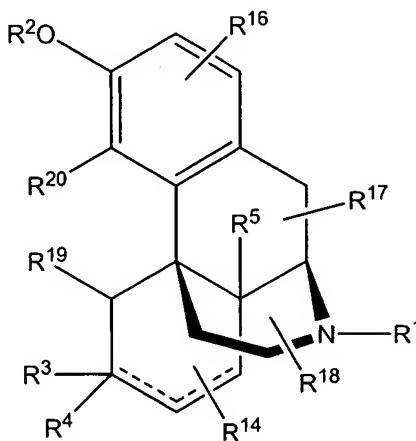


**Claims:**

1. A pharmaceutically acceptable salt of a codrug, wherein the codrug comprises:
  - a) a first drug moiety having a first biological activity, or a prodrug form thereof, including a basic nitrogen,
  - b) a second drug moiety having a second biological activity, or a prodrug form thereof, and
  - c) a linkage covalently linking said first and second drug moieties to form said codrug, said linkage being cleaved under physiological conditions to regenerate said first and second drug moieties as active agents having said first and second biological activities,wherein the salt of the codrug has a decomposition rate at room temperature at least 50% lower than the decomposition rate of said codrug as a free base.
2. The salt of a codrug according to claim 1, wherein the first drug moiety is an opioid.
3. The salt of a codrug according to claim 1 or 2, wherein the second drug moiety is an antidepressant compound, an analgesic compound, a steroid, a non-steroidal antiinflammatory drug (NSAIDs), an antibiotic compound, an anti-fungal compound, an antiviral compound, an antiproliferative compound, an antiglaucoma compound, an immunomodulatory compound, a cell transport/mobility impeding agent, a cytokine, a peptide, a protein, an antimetabolite compound, an antipsoriatic compound, a keratolytic compound, an anxiolytic compound, an antipsychotic compound, an alpha-blocker compound, an anti-androgen compound, an anticholinergic compound, an adrenergic compound, a purinergic compound, a dopaminergic compound, a vanilloid compound, or an anti-cancer compound.
4. The salt of a codrug according to claim 2, wherein the opioid is morphine or a morphine derivative.

5. The salt of a codrug according to claim 4, wherein the active form of the opioid is represented in the general formula (I):



(I)

5 wherein

$R^1$  represents a hydrogen, a  $C_{1-6}$ -alkyl group, a  $C_{3-6}$ -cycloalkyl- $C_{1-6}$ -alkyl group, a  $C_{1-6}$ -alkenyl group, a  $C_{1-6}$ -alkanoyl group, a  $C_{3-6}$ -cycloalkenyl- $C_{1-6}$ -alkyl group, a  $C_{3-6}$ -cycloalkyl- $C_{1-6}$ -alkanoyl group, a  $C_{3-6}$ -cycloalkenyl- $C_{1-6}$ -alkanoyl group, an Ar- $C_{1-6}$ -alkyl group, or an allyl group;

10  $R^2$  represents H, a  $C_{1-6}$ -alkyl group, or a  $C_{1-6}$ -alkanoyl group;

$R^3$  represents a hydrogen, a  $C_{1-6}$ -alkylthio group, an aryl group, a  $C_{1-6}$ -alkoxycarbonylalkyl group, a  $C_{1-6}$ -alkyl group, a hydroxyl group, an azido group, a  $C_{1-12}$ -alkanoyl group, an amine  $NR^d_2$  wherein  $R^d$  is hydrogen or Ar, or  $C(=O)NH_2$  when  $R^4$  is a hydrogen, or an oxo group or  $=NOH$  when  $R^4$  is  
15 absent;

$R^4$  is absent or represents a hydrogen;

$R^5$  represents a hydrogen, a hydroxyl group, a lower alkyl group, an amine  $NR_aR_b$  wherein  $R_a$  is a hydrogen, alkyl  $C_{1-12}$ , alkenyl  $C_{3-8}$ , cycloalkyl  $C_{3-7}$  alkyl  $C_{1-4}$ , Ar-alkyl  $C_{1-5}$  or Ar-alkenyl  $C_{3-5}$ , provided that  $R_a$  does not contain the system  
20  $-CH=CH-$  attached to the nitrogen atom; and  $R_b$  is hydrogen, alkyl  $C_{1-8}$ , or the group  $COR_c$  wherein  $R_c$  is a hydrogen, alkyl  $C_{1-11}$ , alkenyl  $C_{2-7}$ , Ar, Ar-alkyl  $C_{1-5}$ , Ar-alkenyl  $C_{2-5}$ , cycloalkyl  $C_{3-8}$ , or cycloalkyl  $C_{3-8}$  alkyl  $C_{1-3}$ ;

or  $R^4$  and  $R^5$  taken together represent  $-(CH_2)_2-$ ;

$R^{14}$  represents a hydrogen, a lower alkyl group, a halogen group, or  $-C(-OH)(-R^{15})_2$ ;

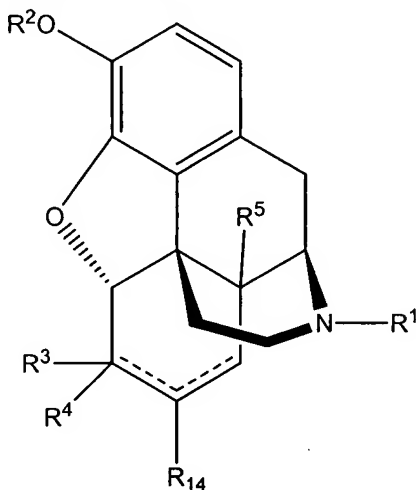
$R^{15}$  independently for each occurrence represents a lower alkyl;

$R^{16}$ ,  $R^{17}$ , and  $R^{18}$  each independently represent a hydrogen, a lower alkyl group, or a halogen group;

$R^{19}$  and  $R^{20}$  each represent hydrogen or together represent the oxygen of a  
5 dihydrofuran ring;

Ar is phenyl or phenyl substituted by halogen, alkyl  $C_{1-3}$ , hydroxyl or alkoxy  $C_{1-3}$ ;  
and the dotted line indicates an optional bond.

6. The salt of a codrug according to claim 4, wherein the active form of the opioid is represented in the general formula (II):



10

(II)

wherein

$R^1$  represents a hydrogen, a  $C_{1-6}$ -alkyl group, a  $C_{3-6}$ -cycloalkyl- $C_{1-6}$ -alkyl group, a  
 $C_{1-6}$ -alkenyl group, a  $C_{1-6}$ -alkanoyl group, a  $C_{3-6}$ -cycloalkenyl- $C_{1-6}$ -alkyl  
15 group, a  $C_{3-6}$ -cycloalkyl- $C_{1-6}$ -alkanoyl group, a  $C_{3-6}$ -cycloalkenyl- $C_{1-6}$ -  
alkanoyl group, an Ar- $C_{1-6}$ -alkyl group, or an allyl group;

$R^2$  represents a hydrogen, a  $C_{1-6}$ -alkyl group, or a  $C_{1-6}$ -alkanoyl group;

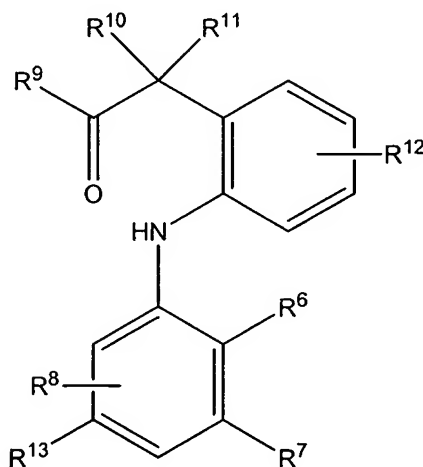
$R^3$  represents a hydrogen, a  $C_{1-6}$ -alkylthio group, an aryl group, a  $C_{1-6}$ -  
alkoxycarbonylalkyl group, a  $C_{1-6}$ -alkyl group, a hydroxyl group, an azido  
20 group, a  $C_{1-12}$ -alkanoyl group, an amine  $NR^d_2$  wherein  $R^d$  is hydrogen or Ar,  
or  $C(=O)NH_2$  when  $R^d$  is a hydrogen, or an oxo group or  $=NOH$  when  $R^d$  is  
absent;

- $R^4$  is absent or represents a hydrogen;
- $R^5$  represents a hydrogen, a hydroxyl group, a lower alkyl group, an amine  $NR_aR_b$  wherein  $R_a$  is a hydrogen, alkyl  $C_{1-12}$ , alkenyl  $C_{3-8}$ , cycloalkyl  $C_{3-7}$  alkyl  $C_{1-4}$ , Ar-alkyl  $C_{1-5}$  or Ar-alkenyl  $C_{3-5}$ , provided that  $R_a$  does not contain the system
- 5         $-CH=CH-$  attached to the nitrogen atom; and  $R_b$  is hydrogen, alkyl  $C_{1-8}$ , or the group  $COR_c$  wherein  $R_c$  is a hydrogen, alkyl  $C_{1-11}$ , alkenyl  $C_{2-7}$ , Ar, Ar-alkyl  $C_{1-5}$ , Ar-alkenyl  $C_{2-5}$ , cycloalkyl  $C_{3-8}$ , or cycloalkyl  $C_{3-8}$  alkyl  $C_{1-3}$ ;
- or  $R^4$  and  $R^5$  taken together represent  $-(CH_2)_2-$ ;
- $R^{14}$  represents a hydrogen, a lower alkyl group, a halogen group, or  $-C(-OH)(-R^{15})_2$ ;
- 10         $R^{15}$  independently for each occurrence represents a lower alkyl;
- Ar is phenyl or phenyl substituted by halogen, alkyl  $C_{1-3}$ , hydroxyl or alkoxy  $C_{1-3}$ ; and the dotted line indicates an optional bond.
7.        The salt of a codrug according to claim 4, wherein the active form of the opioid is selected from apomorphine, buprenorphine, codeine, dihydrocodeine,
- 15        dihydroetorphine, diprenorphine, etorphine, hydrocodone, hydromorphone, levorphanol, meperidine, metopon, o-methylnaltrexone, morphine, naloxone, naltrexone, normorphine, oxycodone, and oxymorphone.
8.        The salt of a codrug according to claim 2, wherein the opioid is fentanyl or a fentanyl derivative.
- 20        9.        The salt of a codrug according to claim 2, wherein the opioid is selected from alfentanil,  $\beta$ -hydroxy-3-methylfentanyl, 4-methoxymethylfentanyl, 4-methylfentanyl, carfentanil, fentanyl, lofentanil, meperidine, remifentanil, and sufentanil.
10.        The salt of a codrug according to claim 2, wherein the active form of the opioid is an analgesic opioid.
- 25        11.        The salt of a codrug according to claim 3, wherein the second drug moiety is an NSAID.

12. The salt of a codrug according to claim 11, wherein the NSAID is selected from piroxicam, diclofenac, etodolac, indomethacin, ketoralac, oxaprozin, tolmetin, naproxen, flubiprofen, fenoprofen, ketoprofen, ibuprofen, mefenamic acid, sulindac, apazone, phenylbutazone, aspirin, celecoxib and rofecoxib, and derivatives thereof.

5 13. The salt of a codrug according to claim 11, wherein the active form of the NSAID is diclofenac or a diclofenac derivative.

14. The salt of a codrug according to claim 11, wherein the active form of the NSAID is represented in the general formula (III):



(III)

wherein

R<sup>6</sup> is a lower alkyl, a lower alkoxy, a fluoro, or a chloro;

R<sup>7</sup> and R<sup>8</sup> are each, independently for each occurrence, a hydrogen, a lower alkyl, a fluoro, a chloro, or a trifluoromethyl;

15 R<sup>9</sup> is OH;

R<sup>10</sup> is a hydrogen or a lower alkyl;

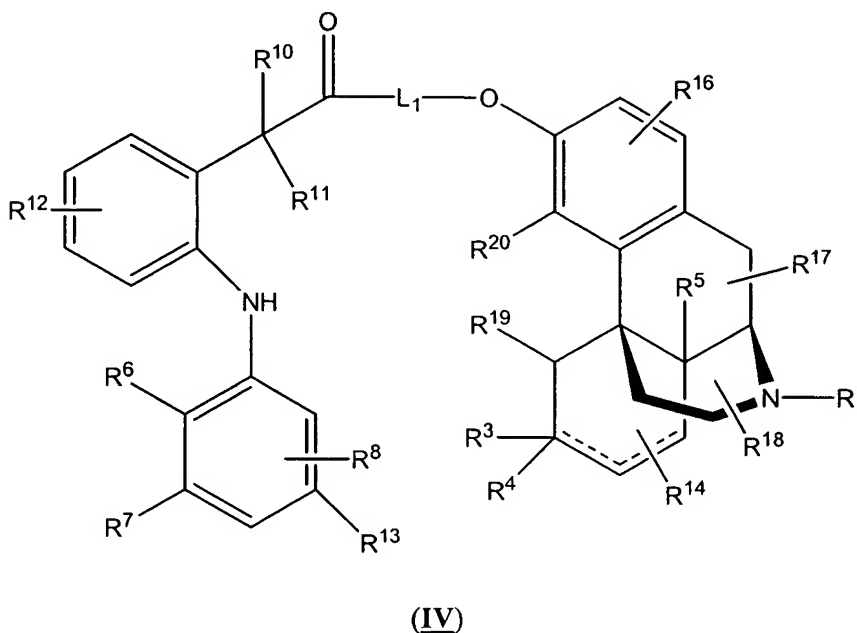
R<sup>11</sup> is a hydrogen, a lower alkyl, or when R<sup>10</sup> is hydrogen, benzyl;

R<sup>12</sup> is a hydrogen, a lower alkyl, a lower alkoxy, a fluoro, a chloro, or a bromo;

R<sup>13</sup> is hydrogen or trifluoromethyl when R<sup>6</sup> is hydrogen or chloro and R<sup>7</sup> is hydrogen or trifluoromethyl.

20

15. The salt of a codrug according to claim 1, wherein the codrug is represented by the general formula (IV):



5            wherein

$L_1$  is absent or represents a linkage;

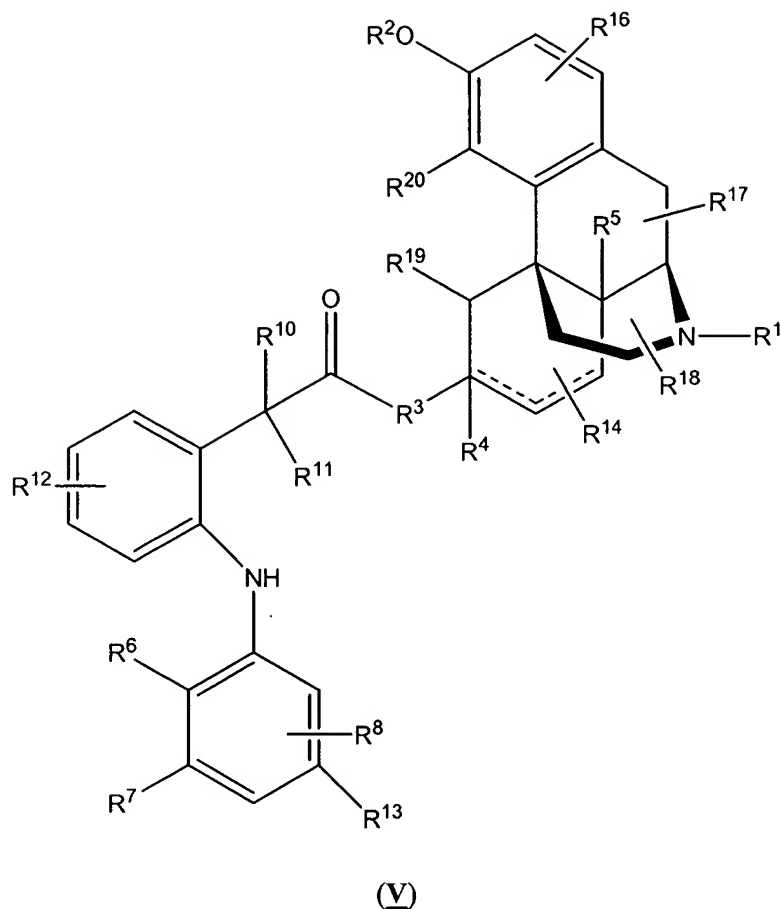
$R^1$  represents a hydrogen, a  $C_{1-6}$ -alkyl group, a  $C_{3-6}$ -cycloalkyl- $C_{1-6}$ -alkyl group, a  $C_{1-6}$ -alkenyl group, a  $C_{1-6}$ -alkanoyl group, a  $C_{3-6}$ -cycloalkenyl- $C_{1-6}$ -alkyl group, a  $C_{3-6}$ -cycloalkyl- $C_{1-6}$ -alkanoyl group, a  $C_{3-6}$ -cycloalkenyl- $C_{1-6}$ -alkanoyl group, an Ar- $C_{1-6}$ -alkyl group, or an allyl group;

$R^3$  represents a hydrogen, a  $C_{1-6}$ -alkylthio group, an aryl group, a  $C_{1-6}$ -alkoxycarbonylalkyl group, a  $C_{1-6}$ -alkyl group, a hydroxyl group, an azido group, a  $C_{1-12}$ -alkanoyl group, an amine  $NR^d_2$  wherein  $R^d$  is hydrogen or Ar, or  $C(=O)NH_2$  when  $R^4$  is a hydrogen, or an oxo group or  $=NOH$  when  $R^4$  is absent;

$R^4$  is absent or represents a hydrogen;

$R^5$  represents a hydrogen, a hydroxyl group, a lower alkyl group, an amine  $NR_aR_b$  wherein  $R_a$  is a hydrogen, alkyl  $C_{1-12}$ , alkenyl  $C_{3-8}$ , cycloalkyl  $C_{3-7}$  alkyl  $C_{1-4}$ , Ar-alkyl  $C_{1-5}$  or Ar-alkenyl  $C_{3-5}$ , provided that  $R_a$  does not contain the system  $-CH=CH-$  attached to the nitrogen atom; and  $R_b$  is hydrogen, alkyl  $C_{1-8}$ , or

- the group  $\text{COR}_c$  wherein  $R_c$  is a hydrogen, alkyl  $\text{C}_{1-11}$ , alkenyl  $\text{C}_{2-7}$ , Ar, Ar-alkyl  $\text{C}_{1-5}$ , Ar-alkenyl  $\text{C}_{2-5}$ , cycloalkyl  $\text{C}_{3-8}$ , or cycloalkyl  $\text{C}_{3-8}$  alkyl  $\text{C}_{1-3}$ ;  
 or  $R^4$  and  $R^5$  taken together represent  $-(\text{CH}_2)_2-$ ;  
 $R^6$  is a lower alkyl, a lower alkoxy, a fluoro, or a chloro;  
 5  $R^7$  and  $R^8$  are each, independently for each occurrence, a hydrogen, a lower alkyl, a fluoro, a chloro, or a trifluoromethyl;  
 $R^{10}$  is a hydrogen or a lower alkyl;  
 $R^{11}$  is a hydrogen, a lower alkyl or when  $R^{10}$  is hydrogen, benzyl;  
 $R^{12}$  is a hydrogen, a lower alkyl, a lower alkoxy, a fluoro, a chloro, or a bromo;  
 10  $R^{13}$  is hydrogen or trifluoromethyl when  $R^6$  is hydrogen or chloro and  $R^7$  is hydrogen or trifluoromethyl;  
 $R^{14}$  represents a hydrogen, a lower alkyl group, a halogen group, or  $-\text{C}(-\text{OH})(-\text{R}^{15})_2$ ;  
 $R^{15}$  independently for each occurrence represents a lower alkyl;  
 $R^{16}$ ,  $R^{17}$ , and  $R^{18}$  each independently represent a hydrogen, a lower alkyl group, or a  
 15 halogen group;  
 $R^{19}$  and  $R^{20}$  each represent hydrogen or together represent the oxygen of a dihydrofuran ring;  
 Ar is phenyl or phenyl substituted by halogen, alkyl  $\text{C}_{1-3}$ , hydroxyl or alkoxy  $\text{C}_{1-3}$ ;  
 and the dotted line indicates an optional bond.
- 20 16. The salt of a codrug according to claim 1, wherein the codrug is represented by the general formula (V):



wherein

- 5  $R^1$  represents a hydrogen, a  $C_{1-6}$ -alkyl group, a  $C_{3-6}$ -cycloalkyl- $C_{1-6}$ -alkyl group, a  $C_{1-6}$ -alkenyl group, a  $C_{1-6}$ -alkanoyl group, a  $C_{3-6}$ -cycloalkenyl- $C_{1-6}$ -alkyl group, a  $C_{3-6}$ -cycloalkyl- $C_{1-6}$ -alkanoyl group, a  $C_{3-6}$ -cycloalkenyl- $C_{1-6}$ -alkanoyl group, an Ar- $C_{1-6}$ -alkyl group, or an allyl group;
- $R^2$  represents a hydrogen, a  $C_{1-6}$ -alkyl group, or a  $C_{1-6}$ -alkanoyl group;
- $R^3$  is absent or represents a linkage;
- 10  $R^4$  is absent or represents a hydrogen;
- $R^5$  represents a hydrogen, a hydroxyl group, a lower alkyl group, an amine  $NR_aR_b$  wherein  $R_a$  is a hydrogen, alkyl  $C_{1-12}$ , alkenyl  $C_{3-8}$ , cycloalkyl  $C_{3-7}$  alkyl  $C_{1-4}$ , Ar-alkyl  $C_{1-5}$  or Ar-alkenyl  $C_{3-5}$ , provided that  $R_a$  does not contain the system  $-CH=CH-$  attached to the nitrogen atom; and  $R_b$  is hydrogen, alkyl  $C_{1-8}$ , or
- 15 the group  $COR_c$  wherein  $R_c$  is a hydrogen, alkyl  $C_{1-11}$ , alkenyl  $C_{2-7}$ , Ar, Ar-alkyl  $C_{1-5}$ , Ar-alkenyl  $C_{2-5}$ , cycloalkyl  $C_{3-8}$ , or cycloalkyl  $C_{3-8}$  alkyl  $C_{1-3}$ ;



or R<sup>4</sup> and R<sup>5</sup> taken together represent  $-(CH_2)_2-$ ;

R<sup>6</sup> is a lower alkyl, a lower alkoxy, a fluoro, or a chloro;

R<sup>7</sup> and R<sup>8</sup> are each, independently for each occurrence, a hydrogen, a lower alkyl, a fluoro, a chloro, or a trifluoromethyl;

5 R<sup>10</sup> is a hydrogen or a lower alkyl;

R<sup>11</sup> is a hydrogen, a lower alkyl or when R<sup>10</sup> is hydrogen, benzyl;

R<sup>12</sup> is a hydrogen, a lower alkyl, a lower alkoxy, a fluoro, a chloro, or a bromo;

R<sup>13</sup> is hydrogen or trifluoromethyl when R<sup>6</sup> is hydrogen or chloro and R<sup>7</sup> is hydrogen or trifluoromethyl;

10 R<sup>14</sup> represents a hydrogen, a lower alkyl group, a halogen group, or  $-C(-OH)(-R^{15})_2$ ;

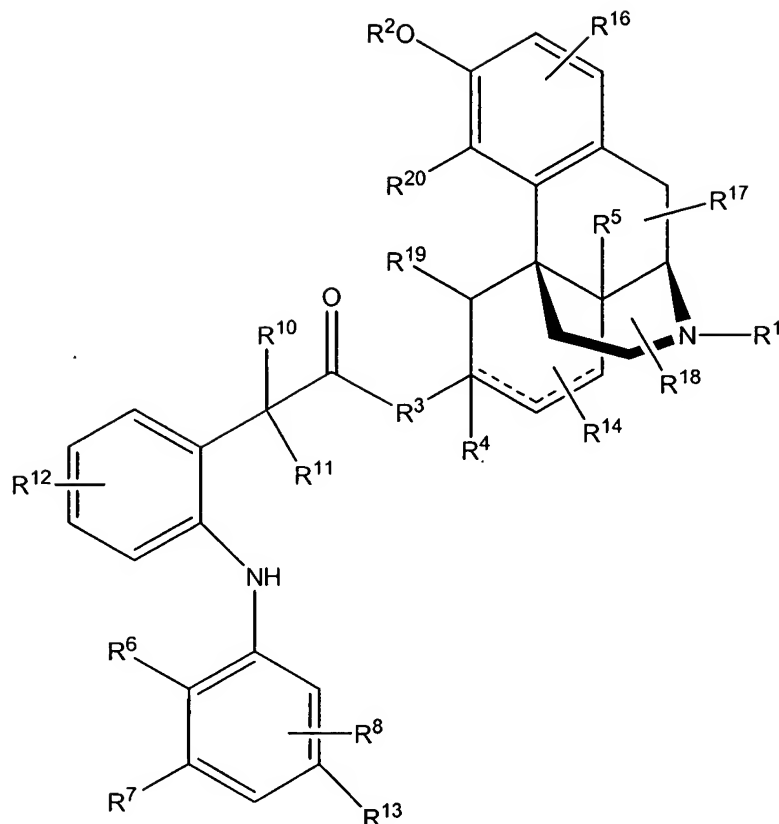
R<sup>15</sup> independently for each occurrence represents a lower alkyl;

R<sup>16</sup>, R<sup>17</sup>, and R<sup>18</sup> each independently represent a hydrogen, a lower alkyl group, or a halogen group;

15 R<sup>19</sup> and R<sup>20</sup> each represent hydrogen or together represent the oxygen of a dihydrofuran ring;

Ar is phenyl or phenyl substituted by halogen, alkyl C<sub>1-3</sub>, hydroxyl or alkoxy C<sub>1-3</sub>; and the dotted line indicates an optional bond.

17. The salt of a codrug according to claim 1, wherein the codrug is represented by the general formula (V):



(V)

wherein

5  $R^1$  represents a hydrogen, a  $C_{1-6}$ -alkyl group, a  $C_{3-6}$ -cycloalkyl- $C_{1-6}$ -alkyl group, a  $C_{1-6}$ -alkenyl group, a  $C_{1-6}$ -alkanoyl group, a  $C_{3-6}$ -cycloalkenyl- $C_{1-6}$ -alkyl group, a  $C_{3-6}$ -cycloalkyl- $C_{1-6}$ -alkanoyl group, a  $C_{3-6}$ -cycloalkenyl- $C_{1-6}$ -alkanoyl group, an Ar- $C_{1-6}$ -alkyl group, or an allyl group;

$R^2$  represents a hydrogen, a  $C_{1-6}$ -alkyl group, or a  $C_{1-6}$ -alkanoyl group;

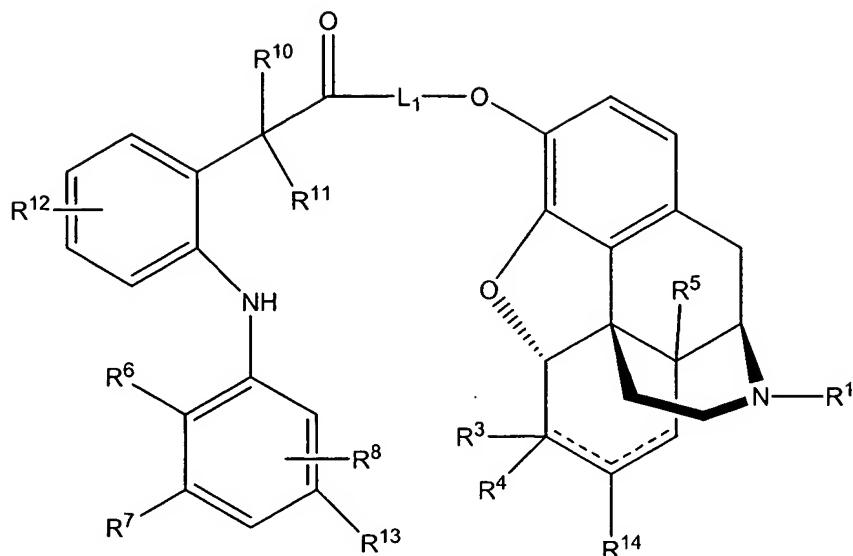
10  $R^3$  represents an oxygen, a  $C_{1-6}$ -alkylthio group, an aryl group, a  $C_{1-6}$ -alkoxycarbonylalkyl group, a  $C_{1-6}$ -alkyl group, an azido group, a  $C_{1-12}$ -alkanoyl group, an amine  $NR^d_2$  (wherein  $R^d$ , independently for each occurrence, is hydrogen, a  $C_{1-6}$ -alkyl group, or Ar),  $-C(=O)NH-$  when  $R^4$  is a hydrogen, or  $=NO-$  when  $R^4$  is absent;

$R^4$  is absent or represents a hydrogen;

15  $R^5$  represents a hydrogen, a hydroxyl group, a lower alkyl group, an amine  $NR_aR_b$  wherein  $R_a$  is a hydrogen, alkyl  $C_{1-12}$ , alkenyl  $C_{3-8}$ , cycloalkyl  $C_{3-7}$  alkyl  $C_{1-4}$ ,

- Ar-alkyl C<sub>1-5</sub> or Ar-alkenyl C<sub>3-5</sub>, provided that R<sub>a</sub> does not contain the system –CH=CH– attached to the nitrogen atom; and R<sub>b</sub> is hydrogen, alkyl C<sub>1-8</sub>, or the group COR<sub>c</sub> wherein R<sub>c</sub> is a hydrogen, alkyl C<sub>1-11</sub>, alkenyl C<sub>2-7</sub>, Ar, Ar-alkyl C<sub>1-5</sub>, Ar-alkenyl C<sub>2-5</sub>, cycloalkyl C<sub>3-8</sub>, or cycloalkyl C<sub>3-8</sub> alkyl C<sub>1-3</sub>;
- 5 or R<sup>4</sup> and R<sup>5</sup> taken together represent –(CH<sub>2</sub>)<sub>2</sub>–;
- R<sup>6</sup> is a lower alkyl, a lower alkoxy, a fluoro, or a chloro;
- R<sup>7</sup> and R<sup>8</sup> are each, independently for each occurrence, a hydrogen, a lower alkyl, a fluoro, a chloro, or a trifluoromethyl;
- R<sup>10</sup> is a hydrogen or a lower alkyl;
- 10 R<sup>11</sup> is a hydrogen, a lower alkyl or when R<sup>10</sup> is hydrogen, benzyl;
- R<sup>12</sup> is a hydrogen, a lower alkyl, a lower alkoxy, a fluoro, a chloro, or a bromo;
- R<sup>13</sup> is hydrogen or trifluoromethyl when R<sup>6</sup> is hydrogen or chloro and R<sup>7</sup> is hydrogen or trifluoromethyl;
- R<sup>14</sup> represents a hydrogen, a lower alkyl group, a halogen group, or –C(–OH)(–R<sup>15</sup>)<sub>2</sub>;
- 15 R<sup>15</sup> independently for each occurrence represents a lower alkyl;
- R<sup>16</sup>, R<sup>17</sup>, and R<sup>18</sup> each independently represent a hydrogen, a lower alkyl group, or a halogen group;
- R<sup>19</sup> and R<sup>20</sup> each represent hydrogen or together represent the oxygen of a dihydrofuran ring;
- 20 Ar is phenyl or phenyl substituted by halogen, alkyl C<sub>1-3</sub>, hydroxyl or alkoxy C<sub>1-3</sub>; and the dotted line indicates an optional bond.

18. The salt of a codrug according to claim 1, wherein the codrug is represented by the general formula **(VI)**:



(VI)

wherein

$L_1$  is absent or represents a linkage;

- 5  $R^1$  represents a hydrogen, a  $C_{1-6}$ -alkyl group, a  $C_{3-6}$ -cycloalkyl- $C_{1-6}$ -alkyl group, a  $C_{1-6}$ -alkenyl group, a  $C_{1-6}$ -alkanoyl group, a  $C_{3-6}$ -cycloalkenyl- $C_{1-6}$ -alkyl group, a  $C_{3-6}$ -cycloalkyl- $C_{1-6}$ -alkanoyl group, a  $C_{3-6}$ -cycloalkenyl- $C_{1-6}$ -alkanoyl group, an Ar- $C_{1-6}$ -alkyl group, or an allyl group;

- 10  $R^3$  represents a hydrogen, a  $C_{1-6}$ -alkylthio group, an aryl group, a  $C_{1-6}$ -alkoxycarbonylalkyl group, a  $C_{1-6}$ -alkyl group, a hydroxyl group, an azido group, a  $C_{1-12}$ -alkanoyl group, an amine  $NR^d$  wherein  $R^d$  is hydrogen or Ar, or  $C(=O)NH_2$  when  $R^4$  is a hydrogen, or an oxo group or  $=NOH$  when  $R^4$  is absent;

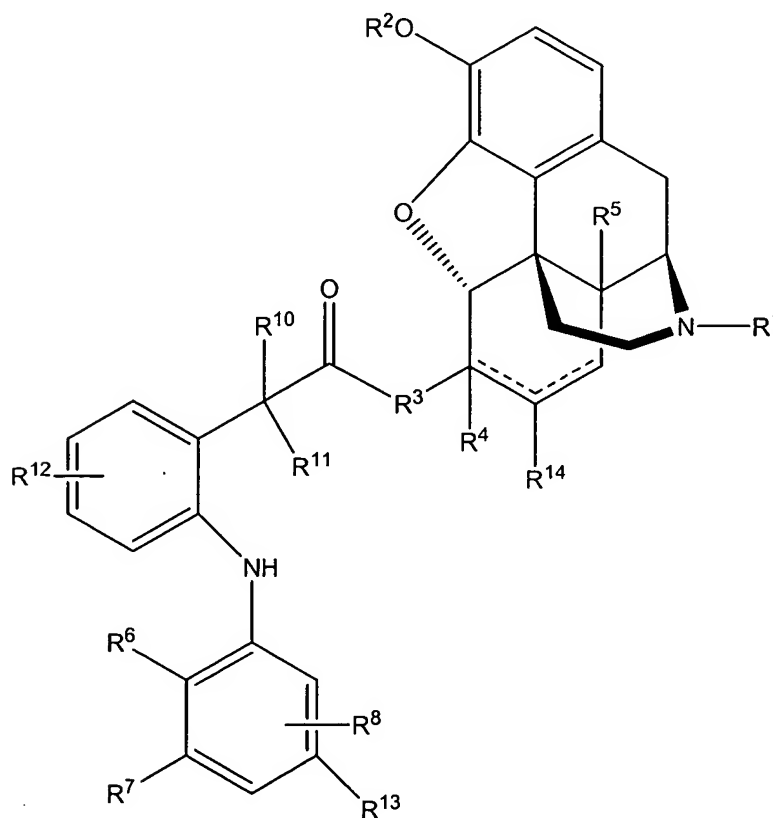
$R^4$  is absent or represents a hydrogen;

- 15  $R^5$  represents a hydrogen, a hydroxyl group, a lower alkyl group, an amine  $NR_aR_b$  wherein  $R_a$  is a hydrogen, alkyl  $C_{1-12}$ , alkenyl  $C_{3-8}$ , cycloalkyl  $C_{3-7}$  alkyl  $C_{1-4}$ , Ar-alkyl  $C_{1-5}$  or Ar-alkenyl  $C_{3-5}$ , provided that  $R_a$  does not contain the system  $-CH=CH-$  attached to the nitrogen atom; and  $R_b$  is hydrogen, alkyl  $C_{1-8}$ , or the group  $COR_c$  wherein  $R_c$  is a hydrogen, alkyl  $C_{1-11}$ , alkenyl  $C_{2-7}$ , Ar, Ar-alkyl  $C_{1-5}$ , Ar-alkenyl  $C_{2-5}$ , cycloalkyl  $C_{3-8}$ , or cycloalkyl  $C_{3-8}$  alkyl  $C_{1-3}$ ;

20 or  $R^4$  and  $R^5$  taken together represent  $-(CH_2)_2-$ ;

- $R^6$  is a lower alkyl, a lower alkoxy, a fluoro, or a chloro;  
 $R^7$  and  $R^8$  are each, independently for each occurrence, a hydrogen, a lower alkyl, a fluoro, a chloro, or a trifluoromethyl;  
 $R^{10}$  is a hydrogen or a lower alkyl;  
 5  $R^{11}$  is a hydrogen, a lower alkyl or when  $R^{10}$  is hydrogen, benzyl;  
 $R^{12}$  is a hydrogen, a lower alkyl, a lower alkoxy, a fluoro, a chloro, or a bromo;  
 $R^{13}$  is hydrogen or trifluoromethyl when  $R^6$  is hydrogen or chloro and  $R^7$  is hydrogen or trifluoromethyl;  
 $R^{14}$  represents a hydrogen, a lower alkyl group, a halogen group, or  $-C(-OH)(-R^{15})_2$ ;  
 10 Ar is phenyl or phenyl substituted by halogen, alkyl  $C_{1-3}$ , hydroxyl or alkoxy  $C_{1-3}$ ;  
 and the dotted line indicates an optional bond.

19. The salt of a codrug according to claim 1, wherein the codrug is represented by the general formula (VII):



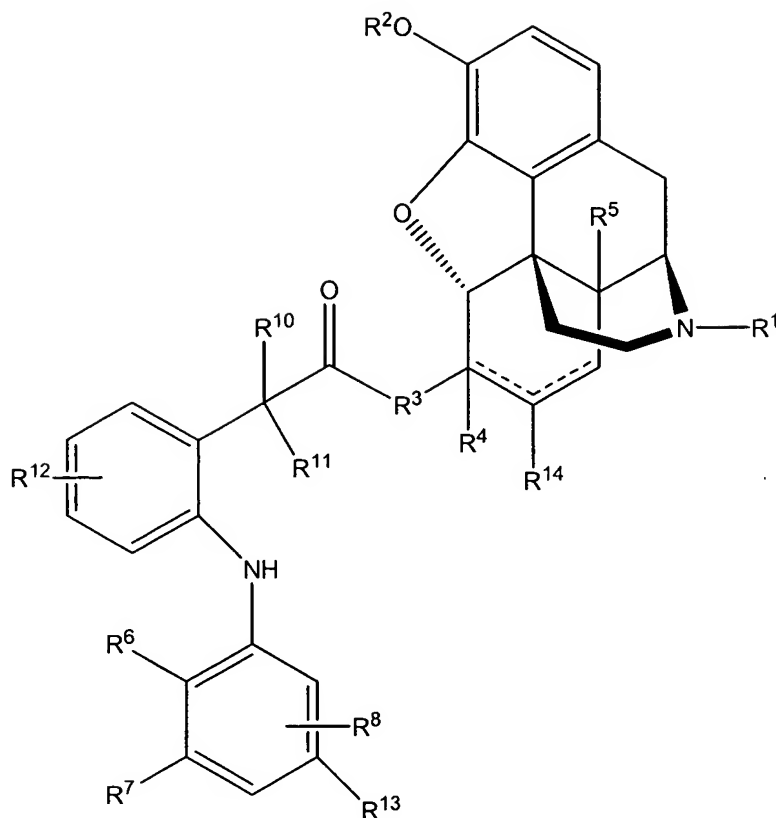
(VII)

15

wherein

- $R^1$  represents a hydrogen, a  $C_{1-6}$ -alkyl group, a  $C_{3-6}$ -cycloalkyl- $C_{1-6}$ -alkyl group, a  $C_{1-6}$ -alkenyl group, a  $C_{1-6}$ -alkanoyl group, a  $C_{3-6}$ -cycloalkenyl- $C_{1-6}$ -alkyl group, a  $C_{3-6}$ -cycloalkyl- $C_{1-6}$ -alkanoyl group, a  $C_{3-6}$ -cycloalkenyl- $C_{1-6}$ -alkanoyl group, an Ar- $C_{1-6}$ -alkyl group, or an allyl group;
- $R^2$  represents a hydrogen, a  $C_{1-6}$ -alkyl group, or a  $C_{1-6}$ -alkanoyl group;
- $R^3$  is absent or represents a linkage;
- $R^4$  is absent or represents a hydrogen;
- $R^5$  represents a hydrogen, a hydroxyl group, a lower alkyl group, an amine  $NR_aR_b$  wherein  $R_a$  is a hydrogen, alkyl  $C_{1-12}$ , alkenyl  $C_{3-8}$ , cycloalkyl  $C_{3-7}$  alkyl  $C_{1-4}$ , Ar-alkyl  $C_{1-5}$  or Ar-alkenyl  $C_{3-5}$ , provided that  $R_a$  does not contain the system  $-CH=CH-$  attached to the nitrogen atom; and  $R_b$  is hydrogen, alkyl  $C_{1-8}$ , or the group  $COR_c$  wherein  $R_c$  is a hydrogen, alkyl  $C_{1-11}$ , alkenyl  $C_{2-7}$ , Ar, Ar-alkyl  $C_{1-5}$ , Ar-alkenyl  $C_{2-5}$ , cycloalkyl  $C_{3-8}$ , or cycloalkyl  $C_{3-8}$  alkyl  $C_{1-3}$ ;
- or  $R^4$  and  $R^5$  taken together represent  $-(CH_2)_2-$ ;
- $R^6$  is a lower alkyl, a lower alkoxy, a fluoro, or a chloro;
- $R^7$  and  $R^8$  are each, independently for each occurrence, a hydrogen, a lower alkyl, a fluoro, a chloro, or a trifluoromethyl;
- $R^{10}$  is a hydrogen or a lower alkyl;
- $R^{11}$  is a hydrogen, a lower alkyl or when  $R^{10}$  is hydrogen, benzyl;
- $R^{12}$  is a hydrogen, a lower alkyl, a lower alkoxy, a fluoro, a chloro, or a bromo;
- $R^{13}$  is hydrogen or trifluoromethyl when  $R^6$  is hydrogen or chloro and  $R^7$  is hydrogen or trifluoromethyl;
- $R^{14}$  represents a hydrogen, a lower alkyl group, a halogen group, or  $-C(-OH)(-R^{15})_2$ ;
- Ar is phenyl or phenyl substituted by halogen, alkyl  $C_{1-3}$ , hydroxyl or alkoxy  $C_{1-3}$ ;
- and the dotted line indicates an optional bond.

20. The salt of a codrug according to claim 1, wherein the codrug is represented by the general formula (VII):



(VII)

wherein

- $R^1$  represents a hydrogen, a  $C_{1-6}$ -alkyl group, a  $C_{3-6}$ -cycloalkyl- $C_{1-6}$ -alkyl group, a  $C_{1-6}$ -alkenyl group, a  $C_{1-6}$ -alkanoyl group, a  $C_{3-6}$ -cycloalkenyl- $C_{1-6}$ -alkyl group, a  $C_{3-6}$ -cycloalkyl- $C_{1-6}$ -alkanoyl group, a  $C_{3-6}$ -cycloalkenyl- $C_{1-6}$ -alkanoyl group, an Ar- $C_{1-6}$ -alkyl group, or an allyl group;
- $R^2$  represents a hydrogen, a  $C_{1-6}$ -alkyl group, or a  $C_{1-6}$ -alkanoyl group;
- $R^3$  represents a  $C_{1-6}$ -alkylthio group, an aryl group, a  $C_{1-6}$ -alkoxycarbonylalkyl group, a  $C_{1-6}$ -alkyl group, an oxygen, an azido group, a  $C_{1-12}$ -alkanoyl group, an amine  $NR^d_2$  (wherein  $R^d$ , independently for each occurrence, is hydrogen, a  $C_{1-6}$ -alkyl group, or Ar),  $-C(=O)NH-$  when  $R^4$  is a hydrogen, or  $=NO-$  when  $R^4$  is absent;
- $R^4$  is absent or represents a hydrogen;
- $R^5$  represents a hydrogen, a hydroxyl group, a lower alkyl group, an amine  $NR_aR_b$  wherein  $R_a$  is a hydrogen, alkyl  $C_{1-12}$ , alkenyl  $C_{3-8}$ , cycloalkyl  $C_{3-7}$  alkyl  $C_{1-4}$ ,

- Ar-alkyl C<sub>1-5</sub> or Ar-alkenyl C<sub>3-5</sub>, provided that R<sub>a</sub> does not contain the system –CH=CH– attached to the nitrogen atom; and R<sub>b</sub> is hydrogen, alkyl C<sub>1-8</sub>, or the group COR<sub>c</sub> wherein R<sub>c</sub> is a hydrogen, alkyl C<sub>1-11</sub>, alkenyl C<sub>2-7</sub>, Ar, Ar-alkyl C<sub>1-5</sub>, Ar-alkenyl C<sub>2-5</sub>, cycloalkyl C<sub>3-8</sub>, or cycloalkyl C<sub>3-8</sub> alkyl C<sub>1-3</sub>;
- 5 or R<sup>4</sup> and R<sup>5</sup> taken together represent –(CH<sub>2</sub>)<sub>2</sub>–;
- R<sup>6</sup> is a lower alkyl, a lower alkoxy, a fluoro, or a chloro;
- R<sup>7</sup> and R<sup>8</sup> are each, independently for each occurrence, a hydrogen, a lower alkyl, a fluoro, a chloro, or a trifluoromethyl;
- R<sup>10</sup> is a hydrogen or a lower alkyl;
- 10 R<sup>11</sup> is a hydrogen, a lower alkyl or when R<sup>10</sup> is hydrogen, benzyl;
- R<sup>12</sup> is a hydrogen, a lower alkyl, a lower alkoxy, a fluoro, a chloro, or a bromo;
- R<sup>13</sup> is hydrogen or trifluoromethyl when R<sup>6</sup> is hydrogen or chloro and R<sup>7</sup> is hydrogen or trifluoromethyl;
- R<sup>14</sup> represents a hydrogen, a lower alkyl group, a halogen group, or –C(–OH)(–R<sup>15</sup>)<sub>2</sub>;
- 15 Ar is phenyl or phenyl substituted by halogen, alkyl C<sub>1-3</sub>, hydroxyl or alkoxy C<sub>1-3</sub>; and the dotted line indicates an optional bond.
21. The salt of a codrug according to claim 17 or 20, wherein R<sup>3</sup> represents a C<sub>1-6</sub>-alkylthio group, an aryl group, a C<sub>1-6</sub>-alkoxycarbonylalkyl group, a C<sub>1-6</sub>-alkyl group, an oxygen, an azido group, a C<sub>1-12</sub>-alkanoyl group, an amine NR<sup>d</sup><sub>2</sub> (wherein
- 20 R<sup>d</sup>, independently for each occurrence, is hydrogen or Ar), –C(=O)NH– when R<sup>4</sup> is a hydrogen, or =NO– when R<sup>4</sup> is absent.
22. The salt of a codrug according to claim 2, wherein the first drug moiety is morphine and the second drug moiety is diclofenac.
23. The salt of a codrug according to claim 1, wherein the linkage is hydrolyzed
- 25 in bodily fluid.
24. The salt of a codrug according to claim 20, wherein the linkage includes one or more hydrolyzable groups selected from an ester, an amide, a carbamate, a carbonate, a cyclic ketal, a thioester, a thioamide, a thiocarbamate, a thiocarbonate, a xanthate and a phosphate ester.



25. The salt of a codrug according to claim 1, wherein the linkage is enzymatically cleaved.
26. The salt of a codrug according to claim 1, wherein the linkage includes a polyethylene glycol, a glycerol, a sugar, an alkylene chain, an amino acid, or an oligopeptide.
27. The salt of a codrug according to claim 1, wherein said codrug salt includes a counterion capable of protonating the basic amine.
28. The salt of a codrug according to claim 1, wherein said codrug salt is formulated from an organic acid.
29. The salt of a codrug according to claim 25, wherein said organic acid is selected from maleic acid, malonic acid, oxalic acid, tartaric acid, citric acid, lactic acid, fumaric acid, benzoic acid, p-toluenesulfonic acid, methanesulfonic acid, acetic acid, adipic acid, formic acid, and salicylic acid.
30. The salt of a codrug according to claim 1, wherein said codrug salt is formulated from an inorganic acid.
31. The salt of a codrug according to claim 27, wherein said inorganic acid is selected from hydrochloric acid, sulfuric acid, hydrobromic acid, nitric acid, and phosphoric acid.
32. The salt of a codrug according to claim 1, wherein the salt of the codrug has a decomposition rate at room temperature less than 10% of the decomposition rate of said codrug as a free base.
33. The salt of a codrug according to claim 1, wherein the salt of the codrug has a decomposition rate at room temperature less than 1% of the decomposition rate of said codrug as a free base.

34. The salt of a codrug according to claim 1, wherein the codrug has an ED<sub>50</sub> for each of said first and second biological activities at least 10 times greater than the ED<sub>50</sub> of said regenerated first and second drug moieties as active agents.
35. The salt of a codrug according to claim 1, wherein the codrug has an ED<sub>50</sub> for each of said first and second biological activities at least 1000 times greater than the ED<sub>50</sub> of said regenerated first and second drug moieties as active agents.
36. The salt of a codrug according to claim 1, which is essentially insoluble in body fluids.
37. The salt of a codrug according to claim 32, wherein said regenerated first and second drug moieties are at least 10 times more soluble than said codrug salt.
38. A malonic acid salt of a codrug comprising morphine covalently linked to diclofenac by a bond which is hydrolyzable to regenerate active morphine and diclofenac *in vivo*.
39. The salt of a codrug according to claim 1, wherein the salt includes the codrug and a pharmaceutically active counterion.
40. A method of manufacturing a salt of a codrug according to claim 1, comprising conjugating an opioid and an NSAID, and crystallizing the codrug salt.
41. A pharmaceutical composition of a codrug salt according to claim 1, wherein the codrug salt is combined with a pharmaceutically acceptable excipient.
42. The salt of a codrug according to claim 1, wherein the codrug salt is dispersed in a hydrogel.
43. The salt of a codrug according to claim 1, wherein the codrug salt has a purity greater than the purity of the codrug as a free base.

44. The salt of a codrug according to claim 40, wherein the codrug salt has a purity of at least 97%.
45. A pharmaceutically acceptable salt of a codrug according to claim 1, wherein at least three drugs are linked to one another covalently.
- 5 46. A pharmaceutically acceptable salt of a codrug according to claim 1, wherein release of the active drugs follows pseudo-zero-order kinetics.
47. A pharmaceutically acceptable salt of a codrug according to claim 1, wherein the drugs are covalently linked and release of the active drugs follows pseudo-zero-order kinetics for about 10 days to about 6 weeks.
- 10 48. A pharmaceutically acceptable salt of a codrug according to claim 44, wherein release of each active drug follows pseudo-zero-order kinetics for about 3 weeks.
49. A pharmaceutically acceptable salt of a codrug according to claim 1, which is soluble in body fluids.
- 15 50. A pharmaceutically acceptable salt of a codrug according to claim 1, wherein said salt form is formulated from an acid that treats at least one symptom of a condition.
51. A method of relieving pain comprising administering an effective amount of a pharmaceutically acceptable salt of a codrug according to claim 1 to a patient in  
20 need of pain relief.
52. The salt of a codrug according to claim 1, wherein the first and second drug moieties are different.
53. The salt of a codrug according to claim 1, wherein the first and second drug moieties are the same.